AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	Group No.:	1634
Serial No.:	09/613,887	Examiner:	J.A. Goldberg
Filed:	07/11/2000		
Entitled:	**METHODS AND COMPOSITIONS FOR PERIOPERATIVE GENOMIC PROFILING**		

TRANSMITTAL OF APPELLANT'S REPLY BRIEF

APPEAL NO.:

Mail Stop Appeal Brief – Patents
Commissioner for Patents
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Date: February 21, 2006

By: Susan M. McClintock
Susan M. McClintock

Madam/Sir:

Submitted herewith in triplicate is the Appellant's Reply Brief to the Examiner's Answer Mailed December 22, 2005, to the Appellant's Appeal Brief filed June 7, 2005.

It is believed no additional fees are due at this time. However, if this is incorrect, the Commissioner is hereby authorized to charge payment of the required fees, and/or credit any overpayment, to **Deposit Account No. 08-1290. Please reference Attorney Docket No. HOGAN-04448 when charging the Deposit Account. An originally executed duplicate of this Transmittal is enclosed for this purpose.**

Dated: February 21, 2006

David A. Casimir
Registration No. 42,295

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
(608) 218-6900

PATENT
Attorney Docket No.: **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	Group No.:	1634
Serial No.:	09/613,887	Examiner:	J.A. Goldberg
Filed:	July 11, 2000		
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**		

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This Brief is transmitted in triplicate. [37 C.F.R. § 1.192(a)].

ARGUMENT

I. Issue

Whether Claims 74-105 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia").

II. Claims 74--105 are Not Obvious Over the Combination of Miller in view of Quane, or in view of Acta and La Du, or in view of Pharmacogenetics and Evans, or in view of Poort, and further in view of Hoon and Hacia.

The present invention claims perioperative genomic profiles comprising assays in two or more nucleic acid markers in two or more genes associated with two or more conditions of use in determining the risk for complications during a surgical procedure. In eight Office Actions over five years of prosecution, the Examiner has raised and withdrawn multiple rejections to these claims. One rejection remains, *i.e.*, whether or not the claims are obvious over the Examiner's combination of nine references. The Examiner alleges that the cited references not only teach all elements of the claims, but that they also provide a suggestion or motivation to combine the references to thereby arrive at the invention. The Appellant asserts that they do not.

The Appellant's Brief recites eighteen elements of the claims (pages 12 – 14) that are nowhere to be found in the Examiner's cited references, either alone or in combination. In

response to the fact of these missing claim elements, the Examiner's Answer attempts, for the first time, to locate and list these elements in the cited art. It fails.

While giving the appearance of an exhaustive listing (Examiner's Answer, pages 16 – 19), the Examiner's inventory neglects to consider, or even mention, missing elements cited by the Appellant in independent Claims 74 ("a genomic profile for use in selecting a perioperative course of action"), 87 ("a genomic profile for use in selecting a surgical treatment course of action"), 94 and 101 ("a genomic profile for use by a physician in determining a risk for complications during a surgical procedure"), and 102 ("an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said assay results are consulted in selecting an appropriate anesthesia treatment" (Appellant's Brief, pages 12 – 13). Moreover, none of the Examiner's cited references teach, contemplate or even mention non-invasive surgery (Claims 76, 96), a medical procedure (Claim 78), a genomic profile for presymptomatic diagnosis (Claim 81), two or more genes associated with two or more conditions (Claims 83 and 91), 5 or more, and 10 or more, mutations for use in selecting a perioperative course of action (Claim 84, 85), selection of conditions for a surgical procedure (Claims 86 and 98), 5 or more, and 10 or more mutations associated with two or more perioperative phenotypes (Claims 92 and 93), selection of dosages of anesthesia (Claim 103), or selection of monitoring procedures (Claim 105).

In tendering these rejections, the Examiner unswervingly fails to read each claim as a whole, engaging instead in impermissible piecemeal analysis of the claim elements. For example, the Examiner argues "The art of record clearly teaches mutations in two or more genes associated with two or more conditions, as discussed above." (Examiner's Answer, page 17). To the contrary, the cited art does not teach, and the Examiner has never identified in the cited art, two or more genes associated with two or more conditions combined to generate a genomic profile for use in selecting a perioperative course of action.

Moreover, the Examiner's Answer falls again into the trap of confusing the benefits of the present invention ("what would have been desirable", Examiner's Answer, page 20) with its alleged obviousness. As pointed out to the Examiner in the Appellant's Brief (page 25), and not responded to in the Examiner's Answer, in *In re Saung Su Lee* the Court of Appeals for the

Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Patent and Trademark Office.[1]

Nor does the Examiner's Answer meet the Patent and Trademark Office's burden to provide a suggestion or motivation to one of skill in the art to combine the elements to yield the claimed invention at the time the invention was made. In seeking to satisfy this absolute requirement for establishing a *prima facie* case of obviousness, the Examiner relies on the reference "Quane". As pointed out on many occasions to the Examiner in the course of prosecution, and again in the Appellant's Brief (page 17), Quane is directed to a single gene, and a single condition, only, and does not address the issue of testing in the perioperative period. Quane tests only those patients who have survived malignant hyperthermia after a previous complicated surgery. Therefore, Quane does not and cannot teach, motivate or suggest a combination of references for obtaining the perioperative genomic profiles of the present invention.

In response, the Examiner's Answer expressly concedes that Quane is directed only to a single gene and single condition, but attempts to bandage a hemorrhaging obviousness rejection in stretching Quane far beyond its explicit and clear-cut limits *i.e.*, "The examiner acknowledges, while the particular teachings of Quane are directed to MH (*i.e.*, "malignant hyperthermia") using genetic information to prevent or avoid certain conditions (sic) is broadly taught by Quane." (Examiner's answer, page 21, emphasis added.) No it is not. To the contrary, Quane does not, in any sense, broadly teach, motivate or suggest a method to prevent or avoid conditions (plural). And, as pointed out in the Appellant's Brief (page 19), the Examiner's novel standard improperly renders all claims drawn to determining a genotype to prevent or avoid a phenotype, obvious and unpatentable after 1994, *i.e.*, the date of the Quane reference. The Examiner's Answer is silent on this point.

The Examiner's restatement of the law does not stop here. In aspiring to meet the Patent and Trademarks Office's legal burden to provide a suggestion or motivation to combine the elements to yield the claimed combination, the Examiner argues: "It is analogous to a person placing their hand on a hot stove. Once they know placing their hand on the hot stove causes a burn or "ouch", it would be obvious to the person not to touch the hot stove unless they wanted

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[1] *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

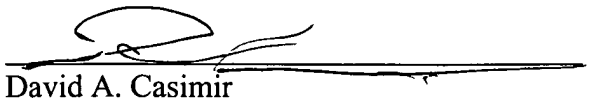
the known result of a burn or "ouch". (Examiner's Answer, page 23.) And: "The Examiner is unclear why the Appellant would not find the preventing death and/or pain and suffering would be a motivation recognized by one of ordinary skill in the art at the time the invention was made." (Examiner's Answer, page 24).

The Examiner's confusion is laid bare. According to the Examiner's interpretation of the law, the Patent and Trademark Office may legally combine any and all elements in establishing a *prima facie* case of obviousness, so long as the invention reduces pain or suffering. As pointed out to the Examiner in the Appellant's Brief (page 20), the Examiner's novel "prevention of death and/or pain and suffering" standard is not the law as expressed in statute, case law or the MPEP. Nor does the Examiner's Answer address, consider or even mention these facts. In turn, the Examiner does not explain why, if the invention is so intuitive and obvious, no one made or used the invention after Quane was published in 1994? The Appellant contends that the motivation to test for a single condition (malignant hyperthermia) associated with a single gene (the ryanodine receptor gene), as in Quane, is most definitely not evidence of motivation to combine the Examiner's references in reconstructing the present invention. Contrary to the Examiner's arguments, the motivation to combine the Examiner's references comes only from the Appellant's disclosure in possession of the Examiner. Nowhere does the Examiner's Answer respond to these contentions as detailed in the Appellant's Brief.

In like vein, the Examiner's Answer fails to address in any way the Appellant's observation (Appellant's Brief, page 30) that Claim 101 is allowable, and has not been examined.

The Appellant asserts that the Examiner's Answer is wrong on the facts, wrong on the law, improperly dismissive of evidence on point, and glaringly deficient in its reasoning. It is submitted that the Examiner's rejection of Claims 74-105 was erroneous, and reversal of the rejection is respectfully requested. The Appellant requests that the Board render a decision as to the allowability of the Claims.

Dated: February 21, 2006



David A. Casimir
Registration No. 42,395

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
(608) 218-6900

APPENDIX A

PENDING CLAIMS

1.-73. (cancelled)

74. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure.

75. (previously presented) The method of Claim 74, wherein said course of action comprises administration of anesthesia during a surgical procedure.

76. (previously presented) The method of Claim 75, wherein said surgical procedure is non-invasive surgery.

77. (previously presented) The method of Claim 75, wherein said surgical procedure is invasive surgery.

78. (previously presented) The method of Claim 74, wherein said course of action comprises administration of anesthesia during a medical procedure.

79. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to a pharmacodynamic risk.

80. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to a pharmacokinetic risk.

81. (previously presented) The method of Claim 74, wherein said genomic profile comprises a presymptomatic diagnosis.

82. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to differential diagnosis of co-existing diseases.

83. (previously presented) The method of Claim 74, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes, said genes selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2*, *F5*, *RYR1*, *CACNA1S*, and *CPT2*.

84. (previously presented) The method of Claim 83, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes.

85. (previously presented) The method of Claim 83, where in said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes.

86. (previously presented) The method of Claim 74, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

87. (previously presented) A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure.

88. (previously presented) The method of Claim 87, wherein said genetic markers are associated with a pharmacological response.

89. (previously presented) The method of Claim 88, wherein said pharmacological response is to an anesthetic.

90. (previously presented) The method of Claim 88, wherein said pharmacological response is to drugs used in anesthetic practice.

91. (previously presented) The method of Claim 87, wherein said two or more nucleic acid genetic markers comprises a mutation in two or more genes associated with two or more conditions, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2.*

92. (previously presented) The method of claim 91, wherein said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

93. (previously presented) The method of claim 91, wherein said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

94. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency, impaired debrisoquine metabolism, thrombosis, and malignant hyperthermia to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

95. (previously presented) The method of Claim 94, wherein said course of action comprises administration of anesthesia during a surgical procedure.

96. (previously presented) The method of Claim 96, wherein said surgical procedure is non-invasive surgery.

97. (previously presented) The method of Claim 96, wherein said surgical procedure is invasive surgery.

98. (previously presented) The method of Claim 94, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

99. (previously presented) The method of Claim 94, wherein the said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

100. (previously presented) The method of Claim 94, wherein the said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

101. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency and impaired debrisoquine metabolism to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

102. (previously presented) A method for selecting an appropriate anesthesia treatment during surgery, comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

a) subjecting said sample to an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said markers are known to be associated with adverse responses to anesthesia treatment;

c) subjecting said subject to a surgical procedure, wherein said assay results are consulted in selecting an appropriate anesthesia treatment for said subject.

103. (previously presented) The method of Claim 102, wherein said selecting comprises selection of dosages of anesthesia.

104. (previously presented) The method of Claim 102, wherein said selecting comprises selection of anesthesia compounds.

105. (previously presented) The method of Claim 102, wherein said selecting comprises selection of monitoring procedures.